REMARKS

1. Claims 1, 2, 10, 12 and 14-18 were rejected under 35 U.S.C. § 103(a) as unpatentable over US 5,725,776 to Kenley et al in view of US 4,780,212 to Kost et al.

2. Applicant submits that independent base claims 1 and 14, and therefore all of the claims that depend from them, distinguish over the combination of Kenley and Kost by delivering ultrasonic energy into the blood and/or dialysate solution within the dialyzer *at a frequency and an intensity sufficient to increase diffusion of molecules across the semipermeable membrane without altering the semipermeable membrane.*

By contrast, the method of Kost operates by temporarily or permanently altering the permeability of a membrane. This operating principle is stated explicitly in the objects of the invention and throughout the entire specification. See, for example, column 2, lines 9-16:

> It is therefore an object of the present invention to provide a method for altering permeability of a membrane to molecules wherein the alteration is totally reversible and can be controlled as to the extent and rate of alteration.
>
> It is a further object of the present invention to provide a method for selectively altering membrane permeability to molecules.

Kost also uses ultrasound to alter the selectivity of a membrane. See column 3, lines 53-57:

> The present invention not only provides controlled movement, but it may be used to make a system in which a molecule moves through a membrane which was previously impermeable.

See also column 4, lines 42-57:

> The ultrasound can be set at an intensity (defined as watts/cm^2) and frequency which results in degradation of the membrane or which produces only reversible changes in the membrane and/or molecules. The preferred frequency range is between 10 kHz and 20 MHz for most membranes and approximately 1 MHz and 3 MHz for biological membranes. The preferred intensity range is between 0.05 and 30 watts/cm^2 for most membranes and between 0.05 and three watts/cm^2 for biological membranes. In general, the duration of the exposure to ultrasound will be limited to avoid excessive temperature rises in either the solution containing the molecule or the membrane. A temperature rise of as little as 2° C. can cause irreversible damage to biological membranes. However, in some uses, irreversible damage to the membrane may be desirable.

Applicant submits that such alterations to the permeability and the selectivity of a membrane are not desirable in the context of hemodialysis treatment. The semipermeable membranes used for hemodialysis treatment are the result of extensive research and testing, and are subject to strict regulation by the U.S. Food and Drug Administration. Altering the permeability or the selectivity of the hemodialysis membrane would be a significant safety concern and for this reason could be very problematic from a regulatory standpoint. This is particularly true in the context of dialyzer reuse, which is practiced at many institutions, because the damage to the membrane could be cumulative over time and may or may not be predictable enough to assure patient safety.

For these reasons, it is preferable to apply an ultrasonic field to the semipermeable hemodialysis membrane at a frequency and intensity sufficient only to increase the rate of diffusion of molecules across the membrane without altering the permeability or the selectivity of the membrane itself. For example, applicant has determined experimentally that an approximately 10-25% increase in the diffusion rate across the semipermeable membrane of a hollow fiber dialyzer can be achieved by applying ultrasonic energy at a frequency of 600 kHz and an intensity of approximately 0.00067 watts/cm^2, which is well below the range described by Kost et al. (A total power of 10 watts of ultrasound energy was applied to a hollow fiber dialyzer with an equivalent membrane area of 1.5 m^2 (15,000 cm^2) and Clearance Rates were measured for Phosphate, B_{12} and Myoglobin.) The increase in efficiency of the dialysis process was greatest for medium to large size molecules (e.g. B_{12} and Myoglobin), showing the potential to overcome a serious limitation that exists with current hemodialysis technologies. It is expected that additional increases in efficiency can be achieved through further optimization of the apparatus and methods.

3. Regarding claims 10, 12 and 18, Examiner has not made a *prima fascia* case for obviousness of the claimed subject matter. The claims recite *an emboli detector for detecting thrombi and emboli entering the chamber from the dialyzer; and an ultrasonic transducer configured to break up thrombi and emboli in the chamber*. By contrast, Kenley only describes ultrasonic air bubble detectors 446 and 486, which have no capability for detecting thrombi (blood clots) and other solid emboli. In addition, the hemodialysis system of Kenley has no

capability for breaking up thrombi or other emboli. On the other hand, Kost only describes the use of ultrasound for separation of aggregated molecules in solution or to disperse clumps of cells or tissue (column 5, lines 41-57) and does not describe any apparatus for detecting or breaking up thrombi or other emboli. Therefore, the combination of Kenley and Kost lacks both the claim limitations and the motivation to combine that are essential for making a rejection under 35 U.S.C. § 103(a).

4. Claims 3 and 4 were rejected under 35 U.S.C. § 103(a) as unpatentable over US 5,725,776 to Kenley et al in view of US 4,780,212 to Kost et al and further in view of DE 37 20 668 A1 to Schael.

5. Claims 3 and 4 are submitted as patentable over the combination of Kenley, Kost and Schael for all of the reasons stated above in relation to base claim 1. Whether considered separately or in combination, Kenley, Kost and Schael fail to disclose a hemodialysis treatment apparatus that delivers ultrasonic energy into the blood and/or dialysate solution within the dialyzer at a frequency and an intensity sufficient to increase diffusion of molecules across the semipermeable membrane without altering the semipermeable membrane.

6. Claims 6-9 were rejected under 35 U.S.C. § 103(a) as unpatentable over US 5,725,776 to Kenley et al in view of US 4,780,212 to Kost et al and further in view of US 6,602,241 to Makower et al.

7. Examiner has not made a *prima fascia* case for obviousness of the claimed subject matter of claims 6-9. Applicant fails to see the relevance of the electrode 52 of Makower, cited by Examiner, to claims 6-9, which recite a waveform generator and various features of the waveform generator. Furthermore, Examiner has made a technical error in equating the electrode 52 of Makower with a waveguide rod. A waveguide rod is significantly different in structure and function from the electrode cited by Examiner. Examiner is invited to clarify the grounds of rejection in a further nonfinal office action.

8. Claims 6-9 were rejected under 35 U.S.C. § 103(a) as unpatentable over US 5,725,776 to Kenley et al in view of US 4,780,212 to Kost et al and further in view of US 5,405,614 to D'Angelo et al.

9. Claims 6-9 are submitted as patentable over the combination of Kenley, Kost and D'Angelo for all of the reasons stated above in relation to base claim 1. Whether considered separately or in combination, Kenley, Kost and D'Angelo fail to disclose a hemodialysis treatment apparatus that delivers ultrasonic energy into the blood and/or dialysate solution within the dialyzer at a frequency and an intensity sufficient to increase diffusion of molecules across the semipermeable membrane without altering the semipermeable membrane.

Furthermore, D'Angelo fails to disclose a waveform generator with circuitry to a provide sweeping frequency sine wave (claim 7), circuitry to vary the frequency within a desired range to find a resonant frequency and to lock onto the resonant frequency (claim 8), or circuitry with a low power setting effective to increase the diffusion rate across the semipermeable membrane of the dialyzer and a high power setting effective to break up thrombus that forms within the dialyzer (claim 9). Examiner erroneously disregarded these apparatus limitations as being a recitation of the intended use of the device. Applicant has amended the claims to clarify that these are apparatus limitations that must be taken into consideration.

10. Claims 11 and 13 were rejected under 35 U.S.C. § 103(a) as unpatentable over US 5,725,776 to Kenley et al in view of US 4,780,212 to Kost et al and further in view of US 6,180,058 to Lindsay et al.

11. Claims 11 and 13 are submitted as patentable over the combination of Kenley, Kost and Lindsay for all of the reasons stated above in relation to base claims 10 and 12. Whether considered separately or in combination, Kenley, Kost and Lindsay fail to disclose a hemodialysis treatment apparatus with an emboli detector for detecting thrombi and emboli entering the chamber from the dialyzer; and an ultrasonic transducer configured to break up thrombi and emboli in the chamber.

12. Applicant notes that no grounds of rejection were provided for claim 5. Applicant therefore assumes that claim 5 must be allowable. New claim 19 recites all of the limitations of original claim 5 in independent form. None of the cited prior art shows a hemodialysis treatment apparatus with a waveguide rod configured to deliver ultrasonic energy from an ultrasonic transducer into a dialyzer. New claims 20-22 are dependent on claim 19.

13. New claim 23 recites a hemodialysis treatment apparatus that includes an ultrasonic transducer and an acoustically reflective surface positioned to create an acoustically resonant structure, which increases the efficiency of the ultrasonic transducer. None of the cited prior art shows these claimed features. New claims 24-26 are dependent on claim 23.

CONCLUSION

Applicant submits that the claims all define novel subject matter that is unobvious. Therefore, allowance of such claims is submitted to be proper and is respectfully requested. If Examiner deems that additional changes are needed prior to allowance of the claims, Examiner is urged to initiate a telephonic interview with applicant's representative at the telephone number listed below.

Very respectfully submitted,

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CLAIMS LISTING

1. (currently amended) Apparatus for hemodialysis treatment, comprising:
a dialyzer having a flow path for a patient's blood and a flow path for a dialysate solution and a semipermeable membrane configured to separate the blood flow path from the dialysate flow path;
and an ultrasonic transducer configured to deliver ultrasonic energy into the blood and/or dialysate solution within the dialyzer at a frequency and an intensity sufficient to increase diffusion of molecules across the semipermeable membrane without altering the semipermeable membrane.

2. (original) The apparatus of claim 1, wherein: the semipermeable membrane of the dialyzer is configured as a hollow fiber membrane.

3. (original) The apparatus of claim 1, further comprising: an acoustic coupling for coupling ultrasonic energy from the ultrasonic transducer into the dialyzer.

4. (original) The apparatus of claim 3, wherein: the dialyzer is configured with a cylindrical body; and the acoustic coupling is configured with two halves, each of the two halves having an approximately semicylindrical cutout configured to fit around the cylindrical body of the dialyzer.

5. (original) The apparatus of claim 1, further comprising: at least one waveguide rod for coupling ultrasonic energy from the ultrasonic transducer into the dialyzer.

6. (original) The apparatus of claim 1, further comprising: an ultrasonic waveform generator connected to the ultrasonic transducer.

7. (currently amended) The apparatus of claim 6, wherein: the ultrasonic waveform generator comprises circuitry for operating in different ~~is switchable between~~ modes, including a narrowband sine wave, a ~~variable or~~ sweeping frequency sine wave and a broadband square or sawtooth waveform, and a switch for selectively switching the ultrasonic waveform generator between operating modes.

8. (currently amended) The apparatus of claim 6, wherein: the ultrasonic waveform generator ~~is configured~~ comprises circuitry to vary the frequency within a desired range to find a resonant frequency and to lock onto the resonant frequency.

9. (currently amended) The apparatus of claim 6, wherein: the ultrasonic waveform generator ~~has~~ comprises circuitry with a low power setting effective to increase the diffusion rate across the semipermeable membrane of the dialyzer and a high power setting effective to break up thrombus that forms within the dialyzer.

10. (original) The apparatus of claim 1, further comprising: a chamber downstream of the dialyzer; an emboli detector for detecting thrombi and emboli entering the chamber from the dialyzer; and an ultrasonic transducer configured to break up thrombi and emboli in the chamber.

11. (original) The apparatus of claim 10, further comprising: a filter configured to prevent thrombi and emboli larger than a predetermined size from entering the patient's circulatory system from the chamber.

12. (original) Apparatus for hemodialysis treatment, comprising: a dialyzer having a flow path for a patient's blood and a flow path for a dialysate solution and a semipermeable membrane configured to separate the blood flow path from the dialysate flow path; a chamber downstream of the dialyzer; an emboli detector for detecting thrombi and emboli entering the chamber from the dialyzer; and an ultrasonic transducer configured to break up thrombi and emboli in the chamber.

13. (original) The apparatus of claim 12, further comprising: a filter configured to prevent thrombi and emboli larger than a predetermined size from entering the patient's circulatory system from the chamber.

14. (currently amended) A method of hemodialysis treatment, comprising: connecting a patient's circulatory system to a dialyzer having a flow path for the patient's blood and a flow path for a dialysate solution and a semipermeable membrane configured to separate the blood flow path from the dialysate flow path; and delivering ultrasonic energy into the <u>blood and/or dialysate solution within the</u> dialyzer<u> at a frequency and an intensity sufficient to increase diffusion of molecules across the semipermeable membrane without altering the semipermeable membrane</u>.

CANCEL 15.

16. (original) The method of claim 14, wherein: ultrasonic energy is delivered into the dialyzer at a power level effective to break up thrombus that forms within the dialyzer.

17. (currently amended) The method of claim 14, wherein: ~~ultrasonic energy is delivered into the dialyzer at a power level effective to increase the diffusion rate across the semipermeable membrane of the dialyzer; and~~ ultrasonic energy is intermittently delivered into the dialyzer at a power level effective to break up thrombus that forms within the dialyzer.

18. (original) The method of claim 14, further comprising: detecting thrombi and emboli entering a chamber downstream of the dialyzer; and energizing an ultrasonic transducer to break up thrombi and emboli in the chamber.

19. (NEW) Apparatus for hemodialysis treatment, comprising:
a dialyzer having a flow path for a patient's blood and a flow path for a dialysate solution and a semipermeable membrane configured to separate the blood flow path from the dialysate flow path;
an ultrasonic transducer; and
at least one waveguide rod configured to deliver ultrasonic energy from the ultrasonic transducer into the blood and/or the dialysate solution within the dialyzer.

20. (NEW) The apparatus of claim 19, wherein the waveguide rod comprises a surface that is textured or faceted to promote uniform dispersion of the ultrasonic energy within the dialyzer.

21. (NEW) The apparatus of claim 19, wherein the waveguide rod is in the configuration of a tapered ultrasonic amplifying horn to increase the amplitude of the ultrasonic waves produced by the ultrasonic transducer.

22. (NEW) The apparatus of claim 19, wherein the ultrasonic transducer and the waveguide rod are configured to deliver ultrasonic energy into the dialyzer at a frequency and an intensity sufficient to increase diffusion of molecules across the semipermeable membrane without altering the semipermeable membrane.

23. (NEW) Apparatus for hemodialysis treatment, comprising:
a dialyzer having a flow path for a patient's blood and a flow path for a dialysate solution and a semipermeable membrane configured to separate the blood flow path from the dialysate flow path;
an ultrasonic transducer configured to deliver ultrasonic energy into the blood and/or the dialysate solution within the dialyzer; and
an acoustically reflective surface positioned opposite to and approximately parallel with the ultrasonic transducer forming an acoustically resonant structure to increase the efficiency of the ultrasonic transducer.

24. (NEW) The apparatus of claim 23, wherein the acoustically reflective surface is backed with a high acoustic impedance material.

25. (NEW) The apparatus of claim 24, wherein the acoustically reflective surface is backed with a low acoustic impedance material.

26. (NEW) The apparatus of claim 24, wherein the dialyzer is configured with a cylindrical body; and wherein the ultrasonic transducer is coupled to the dialyzer body by an acoustic coupling configured with two halves, each of the two halves having an approximately semicylindrical cutout configured to fit around the cylindrical body of the dialyzer, the ultrasonic transducer being located on a first external surface of the acoustic coupling and the acoustically reflective surface located on a second external surface of the acoustic coupling opposite to and approximately parallel with the first external surface of the acoustic coupling.